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(19)(CA) **APPLICATION FOR CANADIAN PATENT** (12)

(54) Use of Guanidine Derivatives for the Preparation of a Pharmaceutical Product Having PNT Antagonistic Activity

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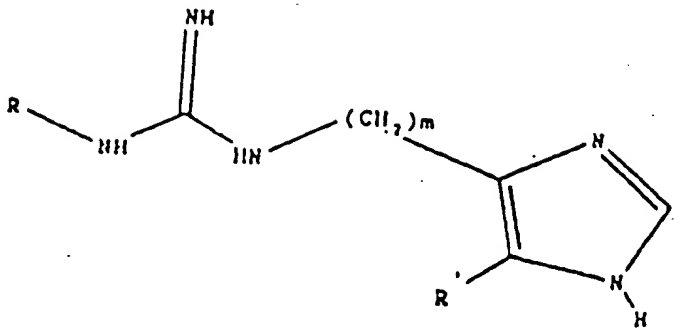
Canada

Abstract

The use of guanidine derivatives having the following basic structure



(II)

for the preparation of a pharmaceutical product having NPY-antagonistic action and in particular for the preparation of a pharmaceutical product for the treatment of high blood pressure is described.

The use of guanidine derivatives for the preparation of a pharmaceutical product having NPY antagonistic activity

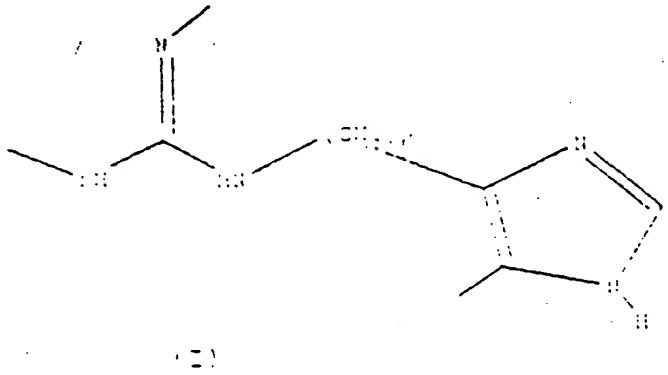
Description

Neuropeptide Y (NPY) is a peptide of 36 amino acids which was originally isolated from pigs' brains (K. Tatemoto, Proc. Natl. Sci., USA 79, 5485 (1982)) but has also been found in the human central and peripheral nervous system.

NPY controls the vascular sympathetic tone together with noradrenalin. The systematic use of NPY leads to prolonged rise in the vascular resistance. Boublik et al (J.H. Boublik, N.A. Scott, M.R. Brown and J.E. Rivier, J. Med Chem. 32, 597 (1989)) also proved the participation of NPY in the production of high blood pressure.

NPY antagonists therefore constitute a potential new method in the treatment of high blood pressure, but no NPY antagonists have hitherto been known.

Guanidine derivatives having the following basic structure

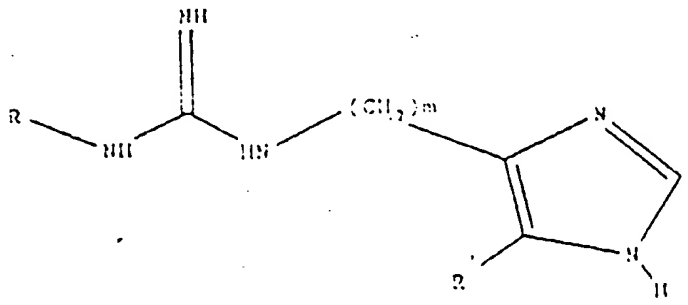


(I)

which have histamine-H_2 agonistic and histamine-H_1 antagonistic activities are known from DE-OS 35 12 084, 35 28 214, 35 28 215 and 36 31 334 and from EP-OS 0 199 845. According to the information given in the said documents, these compounds are suitable, by virtue of their pharmacological properties, for use as cardiotonic agents, i.e. compounds which increase the force of contraction of the heart. They are therefore proposed for the therapy of acute and chronic cardiac insufficiency.

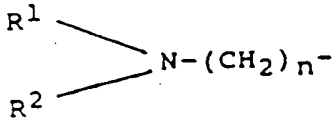
It has now been found that the compounds described above surprisingly also have neuropeptide-Y antagonistic activities independently of the above mentioned cardiotonic and positive inotropic activity.

The present invention therefore relates to the use of guanidine derivatives corresponding to the general formula II



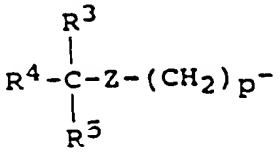
(II)

in which R denotes the group



wherein R^1 denotes a phenyl group which may be unsubstituted or mono- or disubstituted with halogen atoms,

C_1-C_3-alkyl groups or C_1-C_3-alkoxy groups, or a pyridine ring which may be unsubstituted or mono- or disubstituted with halogen atoms, C_1-C_3-alkyl groups or C_1-C_3-alkoxy groups, R^2 denotes a hydrogen atom, a C_1-C_3-alkyl group, a phenyl optionally mono- or disubstituted with halogen atoms, C_1-C_3-alkyl groups or C_1-C_3-alkoxy groups, or a benzyl or hetero aryl methyl group which may be unsubstituted or mono- or disubstituted with halogen atoms, C_1-C_3-alkyl groups or C_1-C_3-alkoxy groups, and n has the value 2, 3 or 4,
or in which R denotes the group

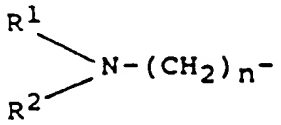


wherein R^3 stands for a pyridine ring or phenyl ring which may be unsubstituted or mono- or disubstituted with halogen atoms, C_1-C_3-alkyl groups or C_1-C_3-alkoxy groups, R^4 denotes a hydrogen atom or a phenyl group optionally mono- or disubstituted with halogen atoms, C_1-C_3-alkyl groups or C_1-C_3-alkoxy groups, R^5 stands for a hydrogen atom or a methyl or hydroxyl group and Z stands for a single bond, an oxygen atom or a sulphur atom, and p has the value 2 or 3,
m has the value 2 or 3 and R' denotes a hydrogen atom or a methyl group,
and the physiologically acceptable salts thereof,
for the preparation of a pharmaceutical product having NPY antagonistic activity.

The substances considered according to the invention are suitable in particular for the treatment of high blood pressure due to their neuropeptide-Y-antagonistic activity.

Another object of this invention is therefore the use of the above-defined guanidine derivatives for the preparation of a pharmaceutical product for the treatment of high blood pressure.

In the general formula II indicated above, R may denote the group



In this group, R^1 stands for an unsubstituted or mono- or disubstituted phenyl group. In the case of substitution, the substituents may in particular be 1 or 2 halogen atoms such as fluorine, chlorine or bromine atoms, preferably fluorine or chlorine atoms, 1 or 2 C_1-C_3-alkyl groups, preferably methyl or ethyl groups, and 1 or 2 C_1-C_3-alkoxy groups such as methoxy or ethoxy groups. Monosubstitution is preferably in the 4-position and disubstitution is preferably in the 3- and 4-position or the 3- and 5-position of the phenyl ring.

The substituent R^1 may also be an unsubstituted or a mono- or disubstituted pyridine ring. Examples of suitable substituents on the pyridine ring include halogen atoms such as fluorine, chlorine or bromine atoms, preferably bromine or chlorine atoms, most preferably bromine atoms, C_1-C_3-alkyl groups such as methyl or ethyl groups and C_1-C_3-alkoxy groups such as methoxy, ethoxy or propoxy groups, preferably methoxy groups.

Linkage of the pyridine ring denoted by R^1 to the nitrogen atom in the group R may take place in the 2-, 3- or 4-position of the pyridine ring, the 2- or 3-position being preferred. Linkage in the 2-position of the pyridine ring is particularly preferred.

R^2 stands for a hydrogen atom, a C_1-C_3-alkyl group, in particular a methyl, ethyl or propyl group, a phenyl

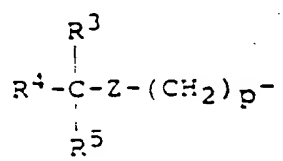
group, which may be unsubstituted or mono- or disubstituted, a benzyl group, which may be unsubstituted or mono- or disubstituted, or a hetero aryl methyl group, which may be unsubstituted or mono- or disubstituted. In the case of substitution, the phenyl group denoted by R^2 may be substituted in the same manner and with the same substituents as described above in connection with the substitution of the phenyl group denoted by R^1.

In the case of substitution, the benzyl group may be substituted with 1 or 2 halogen atoms such as fluorine, chlorine or bromine atoms, preferably chlorine or fluorine atoms, or C_1-C_3-alkoxy groups, such as methoxy or ethoxy groups, preferably methoxy groups. In the case of monosubstitution of the benzyl group denoted by R^2, the substituent is preferably attached in the para position to the methylene group whereas in the case of disubstitution the 3- and 4-positions of the benzyl group are preferred.

When R^2 stands for a hetero aryl methyl group, this group is preferably a thiophenylmethyl, a furanomethyl or a pyridinomethyl group. The heteroarylmethyl group may also be unsubstituted or, preferably, mono- or disubstituted. The substituents may be halogen atoms such as fluorine, chlorine or bromine atoms, C_1-C_3-alkyl groups such as methyl or ethyl groups and linear C_1-C_3-alkoxy groups such as methoxy groups.

The index n has the value 2, 3 or 4, the value 3 being preferred.

R may also stand for the group



In this group, R^3 may denote an unsubstituted or a mono- or disubstituted phenyl group or an unsubstituted or mono- or disubstituted pyridine ring. In the case of substitution, suitable substituents are in particular one or two halogen atoms such as fluorine, chlorine or bromine atoms, preferably fluorine or chlorine atoms, 1 or 2 C_1-C_3-alkyl groups, preferably methyl or ethyl groups, and 1 or 2 C_1-C_3-alkoxy groups, such as methoxy or ethoxy groups. Monosubstitution and disubstitution are preferred. Substitution in the 4-position of the phenyl ring is preferred in the case of monosubstitution and substitution in the 3- and 4-position of the phenyl ring is preferred in the case of disubstitution.

The substituent R^3 may also be an unsubstituted or a mono- or disubstituted pyridine ring, preferably an unsubstituted pyridine ring or a monosubstituted pyridine ring. The substituents of the pyridine ring may be, for example, halogen atoms such as fluorine, chlorine or bromine atoms, preferably bromine or chlorine atoms, most preferably bromine atoms, C_1-C_3-alkyl groups such as methyl or ethyl groups and C_1-C_3-alkoxy groups such as methoxy, ethoxy or propoxy groups, preferably methoxy groups.

Linkage of the pyridine ring denoted by R^3 to the carbon atom in the group R may take place in the 2-, 3- or 4-position of the pyridine ring, the 2- or 3-position being preferred. Linkage in the 2-position of the pyridine ring is particularly preferred.

R^4 denotes a hydrogen atom or an unsubstituted or mono- or disubstituted phenyl group. In the case of substitution, the phenyl group denoted by R^4 is substituted in the same manner as the phenyl group denoted by R^3. R^5 denotes a hydrogen atom or a methyl or hydroxyl group. Z stands for a single bond, an oxygen atom or a sulphur atom and p has the value 2 or 3.

In the general formula II, m has the value 2 or 3,

preferably 3, and R' denotes a hydrogen atom or a methyl group, preferably a hydrogen atom.

According to the invention, it is preferred to use guanidine derivatives corresponding to the above general formula II in which R stands for one of the following groups:

2-(Diphenylmethoxy)ethyl, 2-[bis-(4-fluorophenyl)-methoxy]ethyl,
2-[bis-(4-chlorophenyl)methoxy]ethyl,
3-(4-fluorophenyl)-3-(pyridin-2-yl)propyl,
3-(3,4-difluorophenyl)-3-(pyridin-2-yl)propyl,
3-(3,5-difluorophenyl)-3-(pyridin-2-yl)propyl,
3-(4-chlorophenyl)-3-(pyridin-2-yl)propyl,
3-(3,4-dichlorophenyl)-3-(pyridin-2-yl)propyl,
3-(4-fluorophenyl)-3-(pyridin-3-yl)propyl,
2-[N-(5-bromo-3-methyl-pyridin-2-yl)-benzylamino]ethyl,
2-[N-(5-bromo-3-methyl-pyridin-2-yl)-(4-chlorobenzyl)-amino]-ethyl,
4-(5-bromo-3-methyl-pyridin-2-yl)butyl,
3-(5-bromo-3-methyl-pyridin-2-yl)propyl,
4-(5-bromo-pyridin-2-yl)butyl,
3-(5-bromo-pyridin-2-yl)propyl,
3-(4-chlorophenyl)-3-phenylpropyl,
3-(4-fluorophenyl)-3-phenylpropyl,
3,3-bis-(4-fluorophenyl)propyl or
3,3-bis-(4-chlorophenyl)propyl.

The use of the individual compounds indicated below is particularly preferred:

N^1-[3-(1H-Imidazol-4-yl)propyl]-N^2-[2-[(pyridin-3-yl)methylthio]ethyl]-guanidine
N^1-[3-(1H-imidazol-4-yl)propyl]-N^2-(3,3-diphenylpropyl)-guanidine
N^1-[3-(1H-imidazol-4-yl)]propyl]-N^2-[2-[(pyridin-3-yl)-amino]ethyl]-guanidine
N^1-[3-[(5-bromo-3-methyl-pyridin-2-yl)amino]propyl]-N^2-[3-

(1H-imidazol-4-yl)propyl]-guanidine

N^1-[3-(1H-imidazol-4-yl)propyl]-N^2-[2-(diphenylmethoxy)-ethyl]-guanidine (Compound A)

N^1-[3-(3,5-difluorophenyl)-3-(pyridin-2-yl)propyl]-N^2-[3-(1H-imidazol-4-yl)propyl]-guanidine (Compound B)

N^1-[2-[N-(5-bromo-3-methyl-pyridin-2-yl)-benzylamino]-ethyl]-N^2-[3-(1H-imidazol-4-yl)propyl]-guanidine (Compound C)

N^1-[4-(5-bromo-3-methyl-pyridin-2-yl)butyl]-N^2-[3(1H-imidazol-4-yl)propyl]-guanidine (Compound D).

The compounds used according to the invention are known compounds which may be prepared by the processes described in the above-mentioned documents.

The neuropeptide-Y antagonistic action of the compounds used according to the invention was demonstrated by the method of Motulsky and Michel (H.J. Motulsky, M.C. Michel, Am. J. Physiol. 255, 880 (1988)).

In this method, the rise in intracellular Ca^{++} concentration in HEl cells (human erythroleukemia cells) induced by NPY was measured fluorimetrically, using fura-2 as indicator. Under the given conditions, NPY produces a concentration-dependent rise in the intracellular Ca^{++} concentration by stimulation of the specific NPY receptor.

To measure the inhibitory action of the antagonists to be tested, the latter are added to the incubation medium at concentrations of from 10^{-4} to 10^{-6} and the NPY activity curve is then again determined.

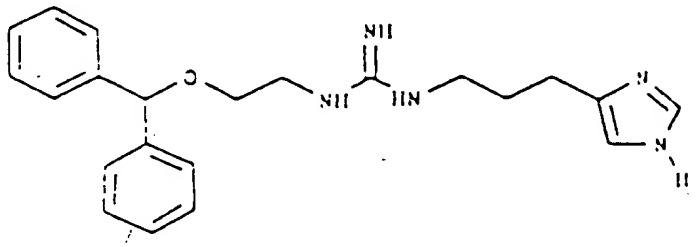
The guanidine compounds used according to the invention shift the NPY concentration activity curve to the right. According to Schild-Plot analysis, the shift to the right is competitive so that the substances antagonise the NPY action by competition on the specific NPY receptor.

The following Table shows the values measured in terms of pA_2 values:

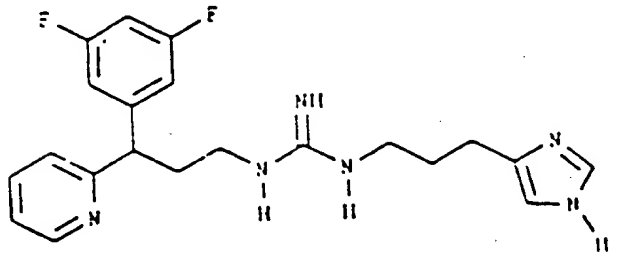
Compound	pA_2 Inhibition of the rise in Ca^{++}
A	4.0
B	4.72
C	5.88
D	5.04

The following compounds were used for the above described test, the results of which are shown in the Table:

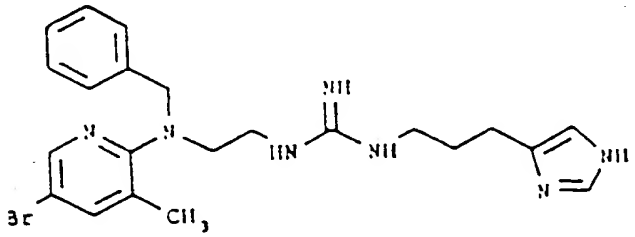
Compound A: N^1-[3-(1H-imidazol-4-yl)propyl]-N^2-[2-(diphenylmethoxy)ethyl]-guanidine



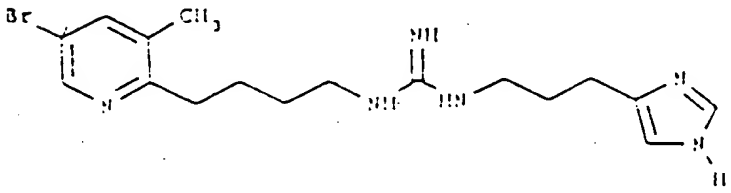
Compound B: N^1-[3-(3,5-difluorophenyl)-3-(pyridin-2-yl)-propyl]-N^2-[3-(1H-imidazol-4-yl)propyl]-guanidine



Compound C: N^1-[2-[N-(5-bromo-3-methyl-pyridin-2-yl)-benzylamino]-ethyl]-N^2-[3-(1H-imidazol-4-yl)-propyl]-guanidine



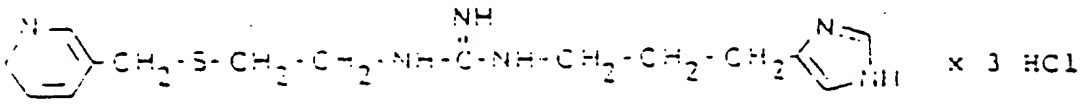
Compound D: N^1-[4-(5-bromo-3-methyl-pyridin-2-yl)butyl]-N^2-[3-(1H-imidazol-4-yl)propyl]-guanidine



The invention is described in the Examples.

Example 1

N^1-[3-(1H-Imidazol-4-yl)propyl]-N^2-[2-[(pyridin-3-yl)-methylthio]-ethyl]guanidine-trihydrochloride



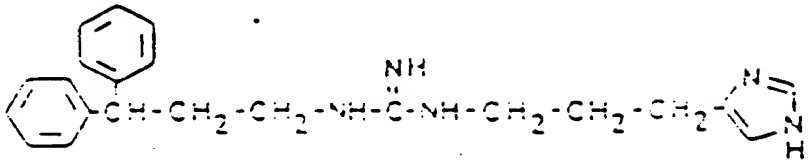
0.85 g (2 mmol) of N-Benzoyl-N'-[3-(imidazol-4-yl)-propyl]-N''-(2-[(pyrid-3-yl)methylthio]ethyl)guanidine are heated under reflux in 45 ml of 18% hydrochloric acid for 6 hours. When the reaction mixture is cold, the benzoic acid formed is removed by extraction with ether, the aqueous phase is evaporated to dryness in a vacuum and the residue is dried in a high vacuum. 0.78 g (91%) of a dry, highly hygroscopic foam is obtained.

$C_{15}H_{22}N_6S \cdot 3HCl$ (427.8)
Molar mass (MS): Calc.: 318.16267; found: 318.16299
MS: m/z (rel. Int. [%]) = 318 (M^+, 3), 168(17), 125(29), 95(31), 93(100), 92(57), 44(89).

^{1}H-NMR data (d_6-DMSO, TMS as internal standard)	δ = 1.87 (m) 2 H,
	2.62 (t) 2 H,
	2.73 (t) 2 H,
	3.0-3.7 (m) 4 H,
	4.10 (s) 2 H,
	7.3 - 8.3 (m) 6 H, 4 H replaceable by D_2O
	8.5 - 9.1 (m) 4 H, ppm.

Example 2

N^1-[3-(1H-Imidazol-4-yl)propyl]-N^2-(3,3-diphenylpropyl)-guanidine-dihydrochloride



x 2 HCl

0.84 g (1.8 mmol) of N-Benzoyl-N'-[3-(imidazol-4-yl)propyl]-N''-(3,3-diphenylpropyl)guanidine are heated under reflux in 45 ml of 20% hydrochloric acid for 7 hours. The product is worked up as in Example 1.
Yield: 0.67 g (86%) of a hygroscopic, non-crystalline solid.

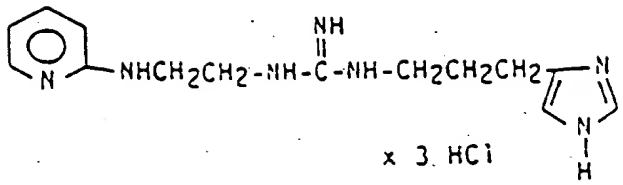
$C_{22}H_{27}N_5 \cdot 2HCl$ (434.4)
MS: m/z (rel. Int. [%]) = 362 ($[M+H]^+$, 84), 167(54), 109(100), 91(60) (FAB method).

^{1}H-NMR data: (d_6-DMSO, TMS as internal standard)

δ = 1.81 (m) 2 H,
2.27 (dt) 2 H,
2.68 (t) 2 H.
3.02 (m) 2 H,
3.16 (m) 2 H,
4.10 (t) 1 H,
7.15 - 7.6 (m) 13 H,
2 H, replaceable by D_2O,
7.80 (m) 2 H,
replaceable by D_2O,
8.99 (d) 1 H, ppm.

Example 3

N^1-[3-(1H-Imidazol-4-yl)propyl]-N^2-[2-(pyridin-2-yl-amino)-ethyl]-guanidine-trihydrochloride



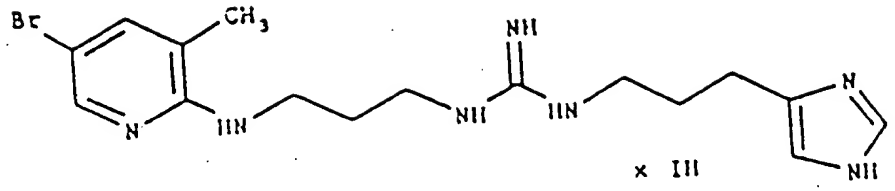
0.93 g (76%) of a colourless, hygroscopic solid are obtained from 1.21 g (3.1 mmol) of N^1-benzoyl-N^2-[3-(1H-imidazol-4-yl)propyl]-N^3-[2-(pyridin-2-yl-amino)-ethyl]-guanidine and 20 ml of conc. hydrochloric acid.

$C_{14}H_{24}Cl_3N_7$ (396.75)

^{1}H-NMR data: (CD_3OD, TMS as internal standard)	δ = 1.80 - 2.21 (m) 2 H,
	2.69 - 3.00 (m) 2 H,
	3.37 (t) 2 H,
	3.57 - 3.83 (m) 4 H,
	4.8 (broad) 8 H, replaceable by D_2O,
	6.96 (t) 1 H,
	7.22 (d) 1 H,
	7.44 (s) 1 H,
	7.83 - 8.16 (m) 2 H,
	8.87 (s) 1 H, ppm.

Example 4

N^1-[3-[(5-Bromo-3-methyl-pyridin-2-yl)amino]-propyl]-N^2-[3-(1H-imidazol-4-yl)propyl]-guanidine-hydroiodide



x III

1.50 g (3.37 mmol) of 3-[(5-Bromo-3-methyl-pyridin-2-yl)amino)propyl]-isothiuronium iodide and 0.42 g (3.37 mmol) of 3-(1H-imidazol-4-yl)propylamine are boiled under reflux in 20 ml of acetonitrile for 3 hours.

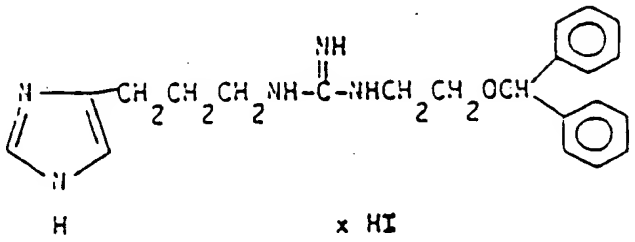
After cooling, the reaction mixture is concentrated by evaporation under vacuum and the residue is purified chromatographically on silica gel, using ethyl acetate/methanol (70:30) as solvent. Concentration of the main fraction by evaporation under vacuum yields 0.41 g (23%) of a colourless, amorphous solid.

$C_{16}H_{25}BrIN_7$ (522.24)

^{1}H-NMR data:	δ = 1.93 (m) 4 H
(CD_3OD, TMS as	2.12 (s) 3 H
internal standard	2.69 (t) 2 H
	3.2 - 3.6 (m) 6 H
	4.9 (broad) 6 H,
	replaceable by D_2O,
	6.95 (s) 1 H
	7.40 (d) 1 H
	7.69 (s) 1 H
	7.93 (d) 1 H, ppm.

Example 5

N^1-[3-(1H-Imidazol-4-yl)propyl]-N^2-[2-(diphenylmethoxy)-ethyl]-guanidine-hydroiodide



x HI

a) N^1-Benzoyl-N^2-[2-(diphenylmethoxy)ethyl]-thiourea

7.8 g (34 mmol) of 2-(diphenylmethoxy)-ethylamine and 5.6 g (34 mmol) of benzoyl isothiocyanate are stirred in 60 ml of ethyl acetate for 2 hours at room temperature. The precipitated solid is suction filtered, washed with ethyl acetate and recrystallised from ethanol. 11.1 g (83%) of colourless crystals, m.p.126-127·C, are obtained.

$C_{23}H_{22}N_2O_2S$ (390.5)

b) S-Methyl-N-[2-(diphenylmethoxy)ethyl]-isothiuronium iodide

11.1 g (28 mmol) of N^1-benzoyl-N^2-[2-(diphenyl-methoxy)ethyl]-thiourea are boiled up with 4.15 g (30 mmol) of potassium carbonate in 200 ml of methanol and 60 ml of water for 40 minutes. After removal of the solvent by evaporation under vacuum, the residue is taken up with 20 ml of water and the aqueous phase is extracted four times with 30 ml of dichloromethane. The combined organic phases are dehydrated with sodium sulphate, filtered and concentrated by evaporation under vacuum. The residue is taken up with 100 ml of ethanol and with 2.1 ml (33 mmol) methyl iodide

stirred up for 20 hours at room temperature. 11.4 g (94%) of a colourless, highly viscous oil are obtained after removal of the solvent by evaporation under vacuum.

$C_{17}H_{21}IN_2OS$ (428.3)

c) N^1-[3-(1H-Imidazol-4-yl)propyl]-N^2-[2-(diphenyl methoxy)ethyl]-guanidine hydroiodide

1.73 g (4 mmol) of S-methyl-N-[2-(diphenylmethoxy)-ethyl]-isothiuronium iodide and 0.50 g (4 mmol) of 3-(1H-imidazol-4-yl)-propylamine are boiled under reflux in 20 ml of acetonitrile for 3 hours. After removal of the solvent by evaporation under vacuum and chromatographic purification on silica gel, using dichloromethane/methanol (80:20) of solvent, 1.41 g (70%) of a colourless, amorphous solid are obtained.

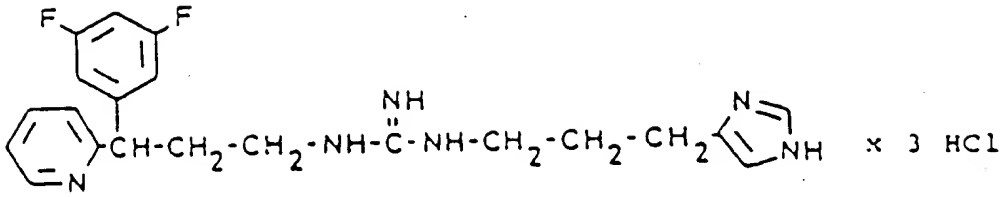
$C_{22}H_{28}IN_5O$ (505.4)

^1H-NMR data: (CD_3OD, TMS as internal standard)

δ = 1.7 - 2.1 (m) 2 H,
2.7 (t) 2 H,
3.1 - 3.8 (m) 6 H
4.9 (broad) 5 H, replaceable by D_2O,
5.6 (s) 1 H,
7.0 (s) 1 H,
7.2 - 7.6 (m) 10 H
8.0 (s) 1 H, ppm.

Example 6

N^1-[3-(3,5-Difluorophenyl)-3-(pyridin-2-yl)propyl]-N^2-[3-(1H-imidazol-4-yl)propyl]guanidine-trihydrochloride



a) N^1-Benzoyl-N^2-[3-(3,5-difluorophenyl)-3-(pyridin-2-yl)-propyl]-N^3-[3-(1H-imidazol-4-yl)propyl]guanidine

1.24 g of 3-(3,5-Difluorophenyl)-3-(pyridin-2-yl)-propylamine and 1.59 g (5 mmol) of N-benzoyl-diphenyl-imidocarbonate are stirred together with 20 ml of methylene chloride at room temperature for 20 minutes. The solvent is then distilled off under vacuum and the oily residue is taken up with 30 ml of pyridine and is heated to 100°C for 45 minutes after the addition of 0.65 g (5.2 mmol) of 3-(1H-imidazol-4-yl)propylamine. The reaction mixture is concentrated by evaporation under vacuum and the residue is taken up with 5% hydrochloric acid and extracted with ether. It is then made alkaline with ammonia and shaken with methylene chloride and the organic phase is washed with water, dehydrated over sodium sulphate and concentrated by evaporation under vacuum. The reaction product is isolated and purified by preparative layer chromatography on silica gel 60 PF_{254} containing gypsum (Solvent: chloroform/methanol 99.5:0.5, ammoniacal atmosphere). 1.3 g (52%) of a colourless, amorphous solid are obtained after concentration of the eluates by evaporation.

$C_{28}H_{28}F_2N_6O$ (502.6)

^{1}H-NMR data: ($CDCl_3$, TMS as internal standard)

δ = 1.96 (m) 2 H,
2.3 (broad) 1 H,
2.6 - 2.8 (m) 3 H,
3.34 (broad) 2 H,
3.5 (broad) 1 H,
3.9 (broad) 1 H,
4.17 (dd) 1 H,
6.6 - 7.8 (m) 11 H,
8.12 (d) 2 H,
8.58 (d) 1 H,
10.3 - 10.9 (broad) 1 H, replaceable by D_2O, ppm.

b) N^1-[3-(3,5-Difluorophenyl)-3-(pyridin-2-yl)propyl]-N^2-[3-(1H-imidazol-4-yl)propyl]guanidine

0.76 g (1.5 mmol) of N^1-benzoyl-N^2-[3-(3,5-difluorophenyl)-3-(pyridin-2-yl)propyl]-N^3-[3-(1H-imidazol-4-yl)propyl]guanidine are heated under reflux in 40 ml of 20% hydrochloric acid for 10 hours. The hydrochloric acid solution is then extracted three times with ether, concentrated to dryness under vacuum and dried in a high vacuum.

Yield: 0.65 g (85%) of the trihydrochloride in the form of a hygroscopic, amorphous solid.

$C_{21}H_{24}F_2N_6 \cdot 3HCl$ (507.8)

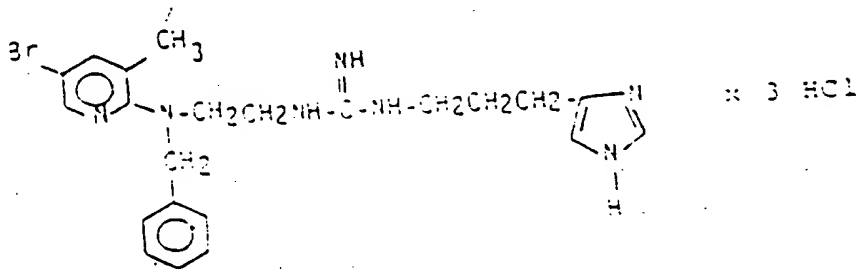
MS (FAB method): m/z (rel. Int. [%]) = 399 ($[M+H]^+$, 80), 232 (100), 204 (13), 109 (60), 100 (36), 95 (11).

^{1}H-NMR data:
(DMSO-d_6, TMS as internal standard)

δ = 1.85 (m) 2 H,
2.35 - 2.65 (m) 2 H,
2.72 (t) 2 H,
3.0 - 3.3 (m) 4 H,
4.78 (t) 1 H.
7.16 (dd) 1 H,
7.36 (d) 2 H,
7.51 (s) 1 H,
7.62 (s) 2 H, replaceable by D_2O,
7.76 (dd) 1 H,
8.02 (m) 3 H, 2 H, replaceable by D_2O,
8.32 (dd) 1 H,
8.75 (d) 1 H,
9.05 (s) 1 H,
14.45 (broad) 1 H, replaceable by D_2O,
14.8 (broad) 1 H, replaceable by D_2O ppm.

Example 7

N^1-[2-[N-(5-Bromo-3-methyl-pyridin-2-yl)-benzylamino]-ethyl]-N^2-[3-(1H-imidazol-4-yl)propyl]guanidine-trihydrochloride



1.15 g (2.0 mmol) of N^1-benzoyl-N^2-[2-[N-(5-bromo-3-methylpyridin-2-yl)-benzylamino]ethyl]-N^3-[3-(1H-imidazol-4-yl)propyl]-guanidine are boiled in 20 ml of conc. hydrochloric acid for 20 hours. The aqueous solution is concentrated by evaporation to about half its volume and extracted with 3 x 20 ml of diethylether.

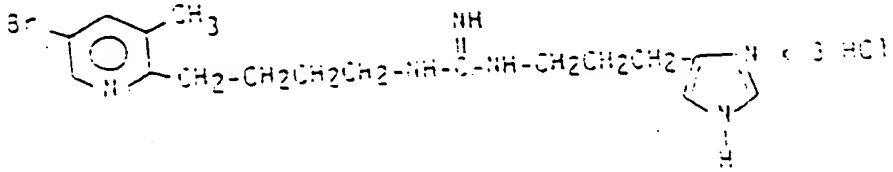
The aqueous phase is then filtered, concentrated to dryness under vacuum and concentrated twice more by evaporation under vacuum, each time with 20 ml of absolute ethanol. The residue is recrystallised from isopropanol. Yield: 0.82 g (71%) of a colourless, highly hygroscopic solid.

$C_{22}H_{31}BrCl_3N_7$ (579.80)

^{1}H-NMR data: (CD_3OD, TMS as internal standard)	δ = 1.80 - 2.18 (m) 2 H 2.61 (s) 3 H, 2.89 (t) 2 H, 3.34 (t) 2 H, 3.60 (m) 2 H, 3.83 (m) 2 H, 4.15 (t) 2 H, 4.9 (broad) 7 H, 7.37 - 7.55 (m) 6 H 8.84 (d) 1 H, 8.92 (d) 2 H, ppm.

Example 8

N^1-[4-(5-Bromo-3-methyl-pyridin-2-yl)butyl]-N^2[3-(1H-imidazol-4-yl)propyl]guanidine-trihydrochloride



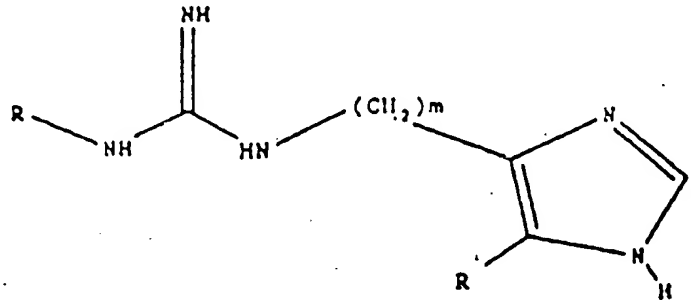
1.00 g (2 mmol) of N^1-Benzoyl-N^2[4-(5-bromo-3-methyl-pyridin-2-yl)butyl]-N^3-[3-(1H-imidazol-4-yl)-propyl]-guanidine are boiled in 20 ml of conc. hydrochloric acid for 18 hours. The aqueous solution, diluted to 40 ml after cooling, is extracted with 4 x 20 ml of diethylether, filtered and concentrated by evaporation under vacuum. The residue is taken up twice with 20 ml of absolute ethanol and concentrated by evaporation. The crude product obtained is then converted into the base with sodium methylate and chromatographed on aluminium oxide, using ethyl acetate/methanol (1:1). The main fraction is taken up with 5 ml of water after concentration by evaporation, 0.5 ml of conc. hydrochloric acid are added and the product is concentrated by evaporation under vacuum. After it has been again concentrated by evaporation with 20 ml of absolute ethanol, 0.62 g (60%) of the title compound are obtained in the form of a colourless, hygroscopic solid.

$C_{17}H_{28}BrCl_3N_6$ (502.71)

^{1}H-NMR data: (CD_3OD, TMS as internal standard)	δ = 1.68 - 2.22 (m) 6 H, 2.61 (s) 3 H, 2.91 (t) 2 H, 3.05 - 3.52 (m) 6H, 4.95 (broad) 7 H, 7.61 (s) 1 H, 8.89 (d) 1 H, 9.10 (d) 2 H, ppm.

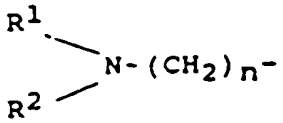
THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. The use of guanidine derivatives corresponding to the general formula II



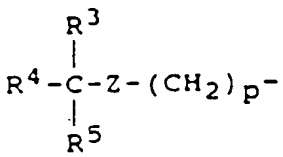
(II)

in which R denotes the group



wherein R^1 stands for a phenyl group which may be unsubstituted or mono- or disubstituted with halogen atoms, C_1-C_3-alkyl groups or C_1-C_3-alkoxy groups or a pyridine ring which may be unsubstituted or mono- or disubstituted with halogen atoms, C_1-C_3-alkyl groups or C_1-C_3-alkoxy groups, R^2 stands for a hydrogen atom, a C_1-C_3-alkyl group, a phenyl group optionally mono- or disubstituted with halogen atoms, C_1-C_3-alkyl groups or C_1-C_3-alkoxy groups, or a benzyl or heteroarylmethyl group which may be unsubstituted or mono- or disubstituted with halogen atoms, C_1-C_3-alkyl groups or C_1-C_3-alkoxy groups, and n has the value 2, 3 or 4,

or in which R denotes the group



wherein R^3 stands for a pyridine ring or phenyl ring which may be unsubstituted or mono- or disubstituted with halogen atoms, C_1-C_3-alkyl groups or C_1-C_3-alkoxy groups, R^4 denotes a hydrogen atom or a phenyl group optionally mono- or disubstituted with halogen atoms, C_1-C_3-alkyl groups or C_1-C_3-alkoxy groups, R^5 stands for a hydrogen atom or a methyl or hydroxy group and Z stands for a single bond, an oxygen atom or a sulphur atom and p has the value 2 or 3, m has the value 2 or 3 and R' denotes a hydrogen atom or a methyl group,
and their physiologically acceptable salts,
for the preparation of a pharmaceutical product having an NPY-antagonistic action.

2. The use according to Claim 1, characterised in that in the general formula II, R stands for one of the following groups:
2-(Diphenylmethoxy)ethyl, 2-[bis-(4-fluorophenyl)-methoxy]-ethyl,
2-[Bis-(4-chlorophenyl)methoxy]ethyl,
3-(4-fluorophenyl)-3-(pyridin-2-yl)propyl,
3-(3,4-difluorophenyl)-3-(pyridin-2-yl)propyl,
3-(3,5-difluorophenyl)-3-(pyridin-2-yl)propyl,
3-(4-chlorophenyl)-3-(pyridin-2-yl)propyl,
3-(3,4-dichlorophenyl)-3-(pyridin-2-yl)propyl,
3-(4-fluorophenyl)-3-(pyridin-3-yl)propyl,
2-[N-(5-bromo-3-methyl-pyridin-2-yl)-benzylamino]ethyl,
2-[N-(5-bromo-3-methyl-pyridin-2-yl)-(4-chlorobenzyl)-amino]-ethyl,
4-(5-bromo-3-methyl-pyridin-2-yl)butyl,
3-(5-bromo-3-methyl-pyridin-2-yl)propyl,
4-(5-bromo-pyridin-2-yl)butyl,
3-(5-bromo-pyridin-2-yl)propyl,
3-(4-chlorophenyl)-3-phenylpropyl,
3-(4-fluorophenyl)-3-phenylpropyl,

3,3-bis-(4-fluorophenyl)propyl or
3,3-bis-(4-chlorophenyl)propyl.

3. The use of N^1-[3-(1H-imidazol-4-yl)propyl]-N^2-[2-[(pyridin-3-yl)methylthio]ethyl]-guanidine and the physiologically acceptable salts thereof for the purpose according to Claim 1.

4. The use of N^1-[3-(1H-imidazol-4-yl)propyl]-N^2-(3,3-diphenylpropyl)guanidine and the physiologically acceptable salts thereof for the purpose according to Claim 1.

5. The use of N^1-[3-(1H-imidazol-4-yl)propyl]-N^2-[2-[(pyridin-2-yl)-amino]ethyl]-guanidine and the physiologically acceptable salts thereof for the purpose according to Claim 1.

6. The use of N^1-[3-[(5-bromo-3-methyl-pyridin-2-yl)-amino]propyl]-N^2-[3-(1H-imidazol-4-yl)propyl]-guanidine and the physiologically acceptable salts thereof for the purpose according to claim 1.

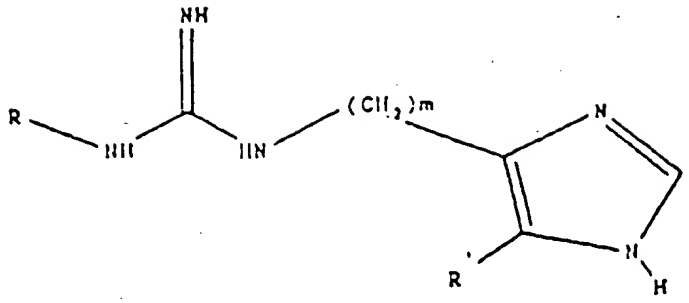
7. The use of N^1-[3-(1H-imidazol-4-yl)propyl]-N^2-[2-(diphenylmethoxy)ethyl]-guanidine and the physiologically acceptable salts thereof for the purpose according to Claim 1.

8. The use of N^1-[3-(3,5-difluorophenyl)-3-(pyridin-2-yl)propyl]-N^2-[3-(1H-imidazol-4-yl)propyl]-guanidine and the physiologically acceptable salts thereof for the purpose according to Claim 1.

9. The use of N^1-[2-[N-(5-bromo-3-methyl-pyridin-2-yl)-benzylamino]-ethyl]-N^2-[3-(1H-imidazol-4-yl)propyl]-guanidine and the physiologically acceptable salts thereof for the purpose according to Claim 1.

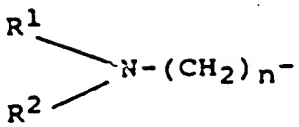
10. The use of N^1-[4-(5-bromo-3-methyl-pyridin-2-yl)butyl]-N^2-[3-(1H-imidazol-4-yl)propyl]-guanidine and the physiologically acceptable salts thereof for the purpose according to Claim 1.

11. The use of guanidine derivatives corresponding to the general formula II



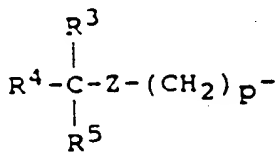
(II)

in which R denotes the group



wherein R^1 stands for a phenyl group which is unsubstituted or mono- or disubstituted with halogen atoms, C_1-C_3-alkyl groups or C_1-C_3-alkoxy groups or a pyridine ring which is unsubstituted or mono- or disubstituted with halogen atoms, C_1-C_3-alkyl groups or C_1-C_3-alkoxy groups, R^2 stands for a hydrogen atom, a C_1-C_3-alkyl group, a phenyl group optionally mono- or disubstituted with halogen atoms, C_1-C_3-alkyl groups or C_1-C_3-alkoxy groups or a benzyl or heteroarylmethyl group which is unsubstituted or mono- or disubstituted with halogen atoms, C_1-C_3-alkyl groups or C_1-C_3-alkoxy groups, and n has the value 2, 3 or 4,

or in which R denotes the group



wherein R^3 stands for a pyridine ring or phenyl ring which is unsubstituted or mono- or disubstituted with halogen atoms, C_1-C_3-alkyl groups or C_1-C_3-alkoxy groups, R^4 denotes a hydrogen atom or a phenyl group optionally mono- or disubstituted with halogen atoms, C_1-C_3-alkyl groups or C_1-C_3-alkoxy groups, R^5 stands for a hydrogen atom or a methyl or hydroxyl group and Z stands for a single bond, an oxygen atom or a sulphur atom and p has the value 2 or 3, m has the value 2 or 3 and R' denctes a hydrogen atom or a methyl group,
and the physiologically acceptable salts thereof
for the preparation of a pharmaceutical product for the treatment of high blood pressure.

12. The use according to Claim 11, characterised in that in the general formula II, R stands for one of the following groups:
2-(Diphenylmethoxy)-ethyl, 2-[bis-(4-fluorophenyl)-methoxy]-ethyl,
2-[bis-(4-chlorophenyl)methoxy]ethyl,
3-(4-fluorophenyl)-3-(pyridin-2-yl)propyl,
3-(3,4-difluorophenyl)-3-(pyridin-2-yl)propyl,
3-(3,5-difluorophenyl)-3-(pyridin-2-yl)propyl,
3-(4-chlorophenyl)-3-(pyridin-2-yl)propyl,
3-(3,4-dichlorophenyl)-3-(pyridin-2-yl)propyl,
3-(4-fluorophenyl)-3-(pyridin-3-yl)propyl,
2-[N-(5-bromo-3-methyl-pyridin-2-yl)-benzylamino]ethyl,
2-[N-(5-bromo-3-methyl-pyridin-2-yl)-(4-chlorobenzyl)-amino]-ethyl,
4-(5-bromo-3-methyl-pyridin-2-yl)butyl,
3-(5-bromo-3-methyl-pyridin-2-yl)propyl,
4-(5-bromo-pyridin-2-yl)butyl,
3-(5-bromo-pyridin-2-yl)propyl,
3-(4-chlorophenyl)-3-phenylpropyl,
3-(4-fluorophenyl)-3-phenylpropyl,

3,3-bis-(4-fluorophenyl)propyl and 3,3-bis-(4-chlorophenyl)propyl.

13. The use of N^1-[3-(1H-imidazol-4-yl)propyl]-N^2-[2-[(pyridin-3-yl)methylthio]ethyl]-guanidine and the physiologically acceptable salts thereof for the purpose according to Claim 11.

14. The use of N^1-[3-(1H-imidazol-4-yl)propyl]-N^2-(3,3-diphenylpropyl)guanidine and the physiologically acceptable salts thereof for the purpose according to Claim 11.

15. The use of N^1-[3-(1H-imidazol-4-yl)propyl]-N^2-[2-[(pyridin-2-yl)amino]-ethyl]-guanidine and the physiologically acceptable salts thereof for the purpose according to Claim 11.

16. The use of N^1-[3-[(5-bromo-3-methyl-pyridin-2-yl)-amino]-propyl]-N^2-[3-(1H-imidazol-4-yl)propyl]-guanidine and the physiologically acceptable salts thereof for the purpose according to Claim 11.

17. The use of N^1-[3-(1H-imidazol-4-yl)propyl]-N^2-[2-(diphenylmethoxy)ethyl]-guanidine and the physiologically acceptable salts thereof for the purpose according to Claim 11.

18. The use of N^1-[3-(3,5-difluorophenyl)-3-(pyridin-2-yl)propyl]-N^2-[3-(1H-imidazol-4-yl)propyl]-guanidine and the physiologically acceptable salts thereof for the purpose according to Claim 11.

19. The use of N^1-[2-[N-(5-bromo-3-methyl-pyridin-2-yl)-benzylamino)ethyl]-N^2-[3-(1H-imidazol-4-yl)propyl]-guanidine and the physiologically acceptable salts thereof for the purpose according to Claim 11.

20. The use of N^1-[4-(5-bromo-3-methyl-pyridin-2-yl)butyl]-N^2-[3-(1H-imidazol-4-yl)propyl]-guanidine and the physiologically acceptable salts thereof for the purpose according to Claim 11.